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Abstract: The importance of environmental factors in the pathogenesis including their disease-modifying potential are increasingly recognized in inflammatory bowel disease (IBD) patients, largely driven by the perception that the prevalence and incidence of IBD are on the rise within the last few years, especially in non-western countries. One of those factors is believed to be hypoxia. The role of hypoxia as a modifying or even causative factor in the genesis and maintenance of inflammation has been increasingly elucidated in recent years. Hypoxia is believed to be a main inducing factor of inflammation. This has been studied in different animal experiments as well as in humans exposed to hypoxia. In several studies - mainly in mice - animals exposed to short-term hypoxia accumulated inflammatory cells in multiple organs and showed elevated cytokines in the blood. Comparable studies were performed in humans, mainly in healthy mountaineers. Recently, we reported on the association between IBD flare-up episodes and antecedent journeys to high-altitude region and aircraft travels. According to these findings, we concluded that flights and stays at high altitudes of >2,000 mg are a risk factor for increased disease activity in IBD. To evaluate the potential influence of hypoxia on the course of IBD on a biomolecular level and to test the effects of hypoxia under standardized conditions, we initiated a prospective and controlled investigation in both healthy controls and IBD patients in stable remission. The study participants underwent a 3-hour exposure to hypoxic conditions simulating an altitude of 4,000 m above sea level in a hyperbaric pressure chamber and clinical parameters as well as blood and stool samples were collected at several time points. The first results of this study are expected in the near future.

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Environmental Triggers for Disease Onset: Can We Avoid Them?

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High Altitude Journeys, Flights and Hypoxia: Any Role for Disease Flares in IBD Patients?

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Key Words

Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · Oxygen supply · Hypoxia · Hypoxemia · High altitude · Pressure chamber · Hypoxia-inducible factors · Inflammation · Autophagy · Inflammasome · Intestinal microbiota · Microbiome

Abstract

The importance of environmental factors in the pathogenesis including their disease-modifying potential are increasingly recognized in inflammatory bowel disease (IBD) patients, largely driven by the perception that the prevalence and incidence of IBD are on the rise within the last few years, especially in non-western countries. One of those factors is believed to be hypoxia. The role of hypoxia as a modifying or even causative factor in the genesis and maintenance of inflammation has been increasingly elucidated in recent years. Hypoxia is believed to be a main inducing factor of inflammation. This has been studied in different animal experiments as well as in humans exposed to hypoxia. In several studies – mainly in mice – animals exposed to short-term hypoxia accumulated inflammatory cells in multiple organs and showed elevated cytokines in the blood. Comparable studies were performed in humans, mainly in healthy mountaineers. Recently, we reported on the association between IBD flare-up episodes and antecedent journeys to high-altitude region and aircraft travels. According to these findings, we concluded that flights and stays at high altitudes of >2,000 mg are a risk factor for increased disease activity in IBD. To evaluate the potential influence of hypoxia on the course of IBD on a biomolecular level and to test the effects of hypoxia under standardized conditions, we initiated a prospective and controlled investigation in both healthy controls and IBD patients in stable remission. The study participants underwent a 3-hour exposure to hypoxic conditions simulating an altitude of 4,000 m above sea level in a hyperbaric pressure chamber and clinical parameters as well as blood and stool samples were collected at several time points. The first results of this study are expected in the near future.

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Background

The crucial role of hypoxia as an inductor of inflammation has been studied extensively in animal experiments as well as in humans exposed to hypoxia. In several studies – mainly in mice – animals exposed to short-term hypoxia accumulated inflammatory cells in multiple organs and showed elevated cytokines in the blood [1–5]. Comparable studies were performed in humans, mainly in healthy mountaineers. One study, for example, investigated healthy volunteers who had spent 3 nights at an elevation of 3,400 m above sea level [6]. In those individuals, an increase of different cytokines such as IL-6, IL-6 receptor and CRP in blood was detected, suggesting an important role of hypoxia in inflammation. Other studies investigated the impact of hypoxia on intestinal transport proteins, sleep, nutrition, exercise capacity, lung function, lipid metabolism and gastric emptying in healthy mountaineers [7–9]. Furthermore, it is well known that exposure to high altitudes may lead to gastric and duodenal erosions and ulcer formation with consecutive gastrointestinal bleeding [10, 11].

Our own group performed a study in which healthy volunteer mountaineers first received an (unsedated) endoscopy at baseline in Zurich. With the sole exception of one subject with reflux esophagitis, all subjects revealed normal endoscopic findings. After that, the study participants went to an altitude of 4,500 above sea level, where 2 further endoscopies were performed. At day 2 (the time of the second endoscopy, performed in 18 subjects), abnormal endoscopic findings were observed in 28% of subjects including hemorrhagic gastritis/duodenitis in 1 subject and duodenal erosions/ulcers in 4 subjects. Strikingly at day 4 (time of third endoscopic examination), the number of endoscopic abnormalities was as high as 61%, that is, 16 out of 23 patients showed signs of gastrointestinal inflammation such as erosions/ulcers in the duodenum or stomach, hemorrhagic gastritis/duodenitis and reflux esophagitis. These results clearly implicate that even in experienced mountaineers hypoxia has profound effects on the gastrointestinal epithelium already after a period of 2 and 4 days, respectively, with exposure to hypoxic conditions [12]. Hypoxia has also been studied as a disease modifying factor and pro-inflammatory stimulus in several disease states, including in IBD, rheumatoid arthritis and cancer [13–18]. Even with regard to solid organ transplantation, hypoxia and consecutive ischemia has been identified as an important driver of inflammation, which ultimately may lead to graft failure [19]. The inter-relationship between hypoxia and inflammation does not appear to be unilateral but rather reciprocal, in that not only hypoxia can promote inflammation but also represent a consequence of the latter, for instance by impairment of blood flow by tissue edema or formation of reactive oxygen species which in turn may lead to oxygen depletion [20]. In the gut, a considerably steep and unique oxygen gradient can be observed in high proximity between the bowel lumen presenting an almost anaerobe compartment toward the highly perfused and oxygen-rich intestinal epithelium [21]. Thus, intestinal epithelial cells are continuously facing hypoxemia in the bowel lumen [20]. The metabolic integrity of the intestinal mucosa is regulated by different effectors, such as intestinal microbiota, blood perfusion to the intestine and tissue oxygenation. However, even in the physiological state, there is a considerable fluctuation in oxygen partial pressure, due to the significant shifts in tissue perfusion for instance in the postprandial state [20]. In general, epithelial barrier integrity and absorptive functions are regulated by oxygen and substantial metabolic shifts are to be observed at sites of mucosal inflammation, where nutritional supply and oxygen are depleted, with consecutive hypoxia, hypoglycemia and lactate accumulation resulting in a decreasing pH [21]. A variety of processes involved in the pathophysiology of inflammation are characterized by a high demand and consumption of oxygen, including cell migration to inflammatory foci [22], phagocytosis [23] and bacterial killing [24] (often mediated by the generation of reactive oxygen species).

Key Messages

As a sequel of decreasing oxygen concentration, the expression of hypoxia-inducible factors (HIFs), present in virtually all human cells, has been well-established. The cells adapt to hypoxia with help of this factor. It exists as a heterodimer with 2 known subunits: HIF-1α or HIF-2α and HIF-1β. HIF is activated in hypoxic conditions but is entirely inactive when oxygen is present [25–28]. In hypoxic conditions, HIF subunits translocate to the nucleus, where they bind as heterodimers to a hypoxia response promoter element, inducing transcription of numerous genes, including those of nuclear factor-κB (NF-κB) and toll-like receptors (fig. 1). In normoxaemic conditions, HIF is targeted by proteosomal degradation. Several effector targets responding to hypoxia have previously been identified, among them targets associated to the generation of ATP, oxidative stress, iron absorption and immune responses [29–36].

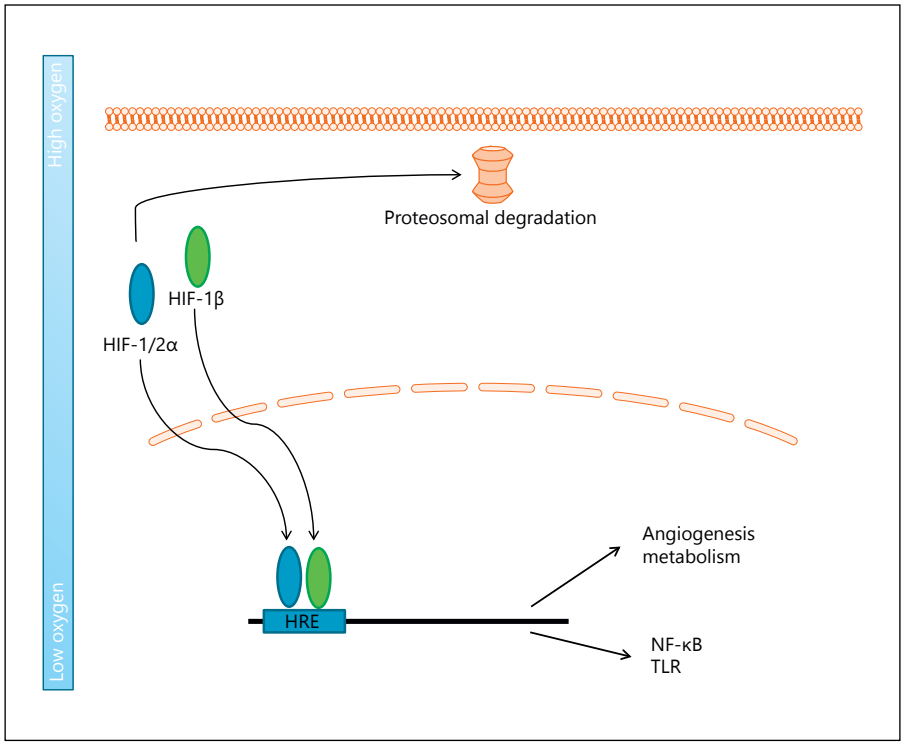

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Fig. 1. Regulation of HIF-1 according to the presence of oxygen. In the presence of oxygen HIF-1α protein is hydroxylated and susceptible to binding to other proteins, such as the E3 ubiquitin ligase VHL (von Hippel Lindau) complex, ultimately leading to proteasomal degradation. In hypoxia, enzymes enabling VHL to bind to HIF-1α are inhibited, precluding attachment of VHL to HIF-1α, which results in stabilization of the latter. Stabilized HIF-1α the may translocate to the nucleus of the cell, where binding with HIF-1β occurs. This binding results in the formation of a heterodimer, which binds to the hypoxia-responsive elements (HREs). The latter contains the core sequence 5'-(A/G)CGTG-3' of the HIF-responsive genes. Among the genes regulated by HRE are those involved in angiogenesis (to increase oxygen supply), metabolism or apoptosis.

Inflammatory bowel disease (IBD) is a chronic, often debilitating intestinal disorder [37, 38]. The etiology of IBD has not yet been fully elucidated; however, results of multiple studies point to a role of dysregulated innate and adaptive immune responses to intestinal bacteria as well as environmental factors, usually subsumized as exposome [39]. In IBDs such as Crohn's disease (CD) and ulcerative colitis (UC), HIF seems also to play a crucial role. Expression of HIF was found to be elevated in inflamed colonic mucosal biopsies of patients with UC and CD on the RNA level [14, 15] as well as on the protein level [16]. HIF appears to stimulate gene expression with regards to proteins involved in the maintenance of epithelial barrier integrity and function [15, 16]. Thus, the transcriptional profile as a sequel of HIF expression ultimately exerts a protective role for the epithelium during inflammation. A mouse model with decreased expression of HIF-1 showed a more severe phenotype of colitis induced by trinitrobenzene sulfuric acid (TNBS), including an increased weight loss and symptoms as well as an increase in epithelial permeability and ultimately mortality, whereas overexpression of HIF revealed to be protective against the TNBS-induced damage [15]. Moreover, the NF-κB, a key factor in the hyperactivation of effector immune cells in the pathogenesis of IBD, seems to be associated to tissue oxygenation, as tissue ischemia and reperfusion was shown to promote its expression in mice [40]. With regard to general intestinal function, both intestinal absorption and permeability were shown to be modified by environmental oxygen concentration [41, 42]. Moreover, hypoxic conditions were shown to directly affect electrical currents when applied to the intestinal tissue from the serosa side [43], suggesting a direct effect of oxygen concentration on ion transport in the gut epithelium. Intriguingly, the induction of 'hypoxia-type' signaling by the inflammatory microenvironment in colitis has been observed, a phenomenon commonly referred to as 'inflammatory hypoxia' [20, 44].

Stimulated by various reports from our IBD patients experiencing increasing disease activity after aircraft travel and high altitude stays, we initiated a retrospective study to investigate a potential epidemiological association between exposure to hypoxia and disease worsening in IBD [45]. In this retrospective study in 103 patients with IBD (50 with CD and 43 with UC), all participants were grouped into those previously having had a flare of disease (52 patients) versus those patients in sustained remission (51 patients). While in the former group 21 patients reported an aircraft travel or a high altitude sojourn (defined as above 2,000 m) within 4 weeks prior to the

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flare, only 8 patients stated such an exposure to high altitude in the latter group with sustained remission. This difference was significant in all IBD patients as well as CD patients, whereas a clear trend could be observed in those with UC. Interestingly, this association appeared to be even more pronounced in long-distant flights (i.e., those above 6 h) as well as in high altitude stays of longer duration and those above 3,000 m [45]. Interestingly, at sea level, the oxygen fraction in the ambient air is roughly 21% with a pressure of 760 mm Hg. During airplane flights, the partial pressure of oxygen in the cabin is neither similar to the ambient pressure present on the altitude of the flight nor ground level, but reduced proportionally to the decrease in air pressure, which is technically maintained in the cabin and not permitted to fall lower than the ambient air pressure at 2,438 m (8,000 ft; equaling 564 mm Hg), as required by international laws [46]. According to systematic investigations, the cabin air pressure during flight virtually always remains in the range between 1,524 m (5,000 ft, 632 mm Hg) and the lowest permitted pressure (equaling 2,438 m ambient air) with a mean pressure value of 604 mm Hg (1,894 m) [47]. This increase in altitude (and decrease in oxygen partial pressure) corresponds to an inspirational oxygen fraction of 15.1% (2,438 m) to 17.1% (1,524 m) at sea level. Consecutively, this decrease in ambient oxygen partial pressure translates into a considerable decrease in the oxygen saturation in the peripheral blood (85 and 91%, respectively) and mean arterial oxygen pressure (53 and 64 mm Hg, respectively), nota bene in healthy volunteers [48]. In healthy subjects, this decrease in oxygen saturation is well tolerated in most instances, whereas hypoxia during aircraft travel may induce discomfort and medical complications in patients with pulmonary diseases [49].

While our study on increased activity in IBD patients after exposure to hypoxia [45] indeed revealed a significant association between inflammation and hypoxia, there are currently no clinical studies available in the literature. No studies have prospectively investigated a potential impact of hypoxia and hypoxemia on the clinical course of disease as well as biomolecular features. To evaluate the potential influence of hypoxia on the course of IBD on a biomolecular level and to test the effects of hypoxia under standardized conditions, we initiated a prospective and controlled investigation in both healthy controls and IBD patients in stable remission. Ten healthy volunteers, 10 CD patients and 10 UC patients underwent a 3-hour exposure to hypoxic conditions simulating an altitude of 4,000 m above sea level in a hyperbaric pressure chamber situated at the Swiss aeromedical centers in Dubendorf, Switzerland. This study had been fully approved by the local ethics committee (EK 2013-0284). Stool samples analyzing calprotectin and microbiotal composition, biopsy samples from the rectosigmoid region and blood samples were repetitively collected and analyzed in conjunction with detailed records of clinical symptoms. At the moment, the study is closed and data are being evaluated. The first results are expected by the middle of 2016.

Conclusion

The importance of environmental factors in the pathogenesis including their disease modifying potential are increasingly recognized in IBD, largely driven by the perception that the prevalence and incidence of IBD are on the rise within the last few years, especially in non-western countries. Not only in these parts of the world, but also in Europe and North America, there have been substantial changes in environmental and life style factors, above all – but not exclusively – with regards to nutritional intake, often referred to as westernization, while the genetic pool has only modestly been subject to changes within that period. So far, the knowledge on the potential role of hypoxia in IBD is only scarce, despite both, numerous investigations in animal models and human, suggesting that hypoxia has a profound influence on the integrity and function of the gastrointestinal tract, epithelial barrier, immune system and microbial composition as well as the increasing body of evidence, that exposure to hypoxia (airline travel and high-altitude stopover) may be associated with various gastrointestinal symptoms and signs and furthermore has an impact on the course of disease in IBD.

Determining the mechanisms underlying these associations and the potential interplay of these factors are crucial to prevent and treat deleterious effects of hypoxia in IBD patients with future high-altitude sojourn. However, hypoxia and hypoxemia may indeed be occurring during exposure to ambient air with normal oxygen partial pressures. For instance, as a result of the altered physiology within the intestinal barrier in patients with IBD exposed to normobaric ambient air local hypoxemia is highly likely to be present, at least intermittently, such as for instance due to increased oxygen extraction as a result of altered metabolic properties in inflammation or impaired oxygen delivery due to alterations in vascular architecture as a sequel of tissue fibrosis, edema or antecedent surgical intervention.

Thus, we consider our proposed research of importance for the general ('sea-level') IBD patient. Understanding molecular and microbiological consequences of intestinal hypoxia may ultimately derive further insights on the pathogenesis of IBD, far beyond exposure to lower partial oxygen pressure ambient air.

Disclosure Statement

The authors declare no disclosures.

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